REMARKS

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claims 1, 3, 13-15, 23, 30, 42, 50, 52, 61, 63, 65, 67, 69, and 71 are amended and claims 24-29, 31-39, and 43-46 are canceled. Therefore, claims 1-23, 30, 40-42, and 47-71 are pending.

Interview Summary

Applicant thanks Examiner Gollamudi S. Kishore for the courtesy of a telephone interview on 29 August 2007, with Inventor Gerard Jensen and Applicant's representative Robert J. Harris. During the interview, the following specific topics were discussed.

Inventor Jensen noted that certain specific gradient methods for loading liposomes are known. These methods allow a higher concentration of an agent to be loaded into liposomes. However, after loading a liposome using an acid gradient, the interior of the liposome has residual acidity that can lower the useful lifetime for an encapsulated agent. Accordingly, there is a need for methods that can be used to provide liposomes that contain a high concentration of drug in a less acidic environment (i.e. an environment that is less destructive for the agent over time). Applicant has discovered a method for preparing such liposomes.

For Example, claim 1 is directed to a method of forming gradient loaded liposomes, the method comprising:

(a) contacting liposomes in an aqueous solution of up to about 60 mM of an acid with an anthracycline chemotherapeutic agent, at a temperature wherein the protonated form of the anthracycline chemotherapeutic agent is charged and is not capable of permeating the membrane of the liposomes, and wherein the unprotonated form of the anthracycline chemotherapeutic agent is uncharged and is capable of permeating the membrane of the liposomes;

(b) actively loading the liposomes with the anthracycline chemotherapeutic agent by raising the pH of the solution to 5.0 or above;

(c) cooling the solution to a temperature at which the unprotonated form of the anthracycline chemotherapeutic agent is not capable of permeating the membrane of the liposomes; and

(d) contacting the solution with a weak base that is an ammonium salt or an alkyl amine, in an amount effective to raise the pH of the internal liposome to provide gradient loaded liposomes.

Additionally, inventor Jensen noted that the resulting liposomes possess an additional advantage: once they are administered to an animal, the weak base (e.g. the ammonium salt or the alkyl amine), can pass back out of the liposome so that the initial pH gradient can be reestablished. This prevents the agent from leaking out of the liposome at too high of a rate following administration. This advantage was not generally understood in the art at the time of Applicant's invention.

Thus, the claimed methods provide liposomes that 1) have high agent loading, 2) can be stored without significant damage to the loaded agent, and 3) regain a higher pH gradient along with longer agent retention following administration (please see the first paragraph of the Summary of the Invention). Such liposomes were not available prior to Applicant's invention.

During the phone interview, the Examiner suggested that the claims be amended to focus on some of the weak bases that are particularly useful for carrying out the methods of the invention. Applicant has amended claims 1, 63, and 71 to recite a weak base that is an ammonium salt or an alkyl amine. These bases are particularly useful for carrying out the methods of the invention, since they can pass through the cooled liposome in step d of the claimed methods to raise the interior pH, and since they can also pass back through the liposome following administration, to reestablish the pH gradient that prevents unwanted leaking of the agent. At the conclusion of the interview, the Examiner suggested that Applicant provide a formal written reply addressing the outstanding rejections.

The above account is believed to be a complete and accurate summary of the topics discussed during the telephonic interview as required by 37 C.F.R. 1.133. If the Examiner believes that this summary is inaccurate or incomplete, Applicant respectfully requests that the Examiner point out any deficiencies in his next communication so that Applicant can amend or supplement the interview summary.

As a preliminary note, claim 3 has been amended to correct a typographical error; dependent claims 13-15, 23, 30, 42, 50, 52, and 61 have been amended to be consistent with amendments made to independent claim 1; and dependent claims 65, 67, and 69 have been amended to be consistent with amendments made to independent claim 63.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 1-71 under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The Examiner's individual grounds for rejection are identified and addressed in the following paragraphs.

At page 2 of the Office Action, the Examiner stated that claim 1 and claim 63 are confusing. This rejection is respectfully traversed.

Claims 1, 63, and 71 have been amended to clarify the process steps recited therein. For example, the claims have been amended to make it clear that the initial liposomes are in an aqueous solution of up to about 60 mM acid. Support for the amendments to these claims can be found from page 12, line 18 through page 14 of the specification, and in the Examples at pages 30-33. These amendments are believed to obviate the Examiner's ground for rejection. Accordingly, withdrawal of the rejection is respectfully requested.

At page 2 of the Office Action, in the last paragraph, the Examiner stated that claim 43 was confusing. Claim 43 has been canceled. Accordingly, this rejection is now moot.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 1-6, 8-26, 28-29, 32, 40-51 and 58-71 under 35 USC § 102(b) as being anticipated by WO 99/13816. This rejection is respectfully traversed.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Dillon*, 919 F.2d 688, 16 U.S.P.Q.2d 1897, 1908 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

As noted by the Examiner at page 3 of the office action, WO 99/13816 discusses certain specific methods for loading campothecins using a pH gradient.

Amended independent claims 1, 63, and 71 all recite an anthracycline chemotherapeutic agent. It is respectfully submitted that WO 99/13816 does not describe liposomes, or methods for producing liposomes, which comprise an anthracycline chemotherapeutic agent. Thus, there is a difference between the claimed invention and the reference disclosure. Accordingly, WO 99/13816 does not anticipate the instant claims. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-44, 47-48, 51 and 58-71 under 35 USC § 103(a) as being unpatentable over EP 0 719 546 or WO 99/13816, by themselves or in combination. These rejections are respectfully traversed.

In order to make a rejection under 35 U.S.C. 103(a) the Examiner first must establish a *prima facie* case of obviousness. Three criteria must be met: 1) there must be some suggestion or motivation, either in the reference or in the knowkedge generally available to one of ordinary skill in the art, to modify the reference; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach all the claim limitations. M.P.E.P. 2142.

Independent claims 1, 63, and 71 recite: (a) contacting liposomes in an aqueous solution of up to about 60 mM of an acid with an anthracycline chemotherapeutic agent, at a temperature wherein the protonated form of the anthracycline chemotherapeutic agent is charged and is not capable of permeating the membrane of the liposomes, and wherein the unprotonated form of the anthracycline chemotherapeutic agent is uncharged and is capable of permeating the membrane of the liposomes; (b) actively loading the liposomes with the anthracycline chemotherapeutic agent by raising the pH of the solution to 5.0 or above; (c) cooling the solution to a temperature at which the unprotonated form of the anthracycline chemotherapeutic agent is not capable of permeating the membrane of the liposomes; and (d) contacting the solution with a weak base that is an ammonium salt or an alkyl amine, in an amount effective to raise the pH of the internal liposome to provide gradient loaded liposomes

EP 0 719 546 discusses gradient loading of liposomes – however, EP 0 719 546 does not disclose a process that includes steps c and d above. Accordingly, EP 0 719 546 does not teach all the elements of the instant claims. Thus, it is respectfully submitted that the instant claims are not *prima facie* obvious over the disclosure of EP 0 719 546. Withdrawal of the rejection of claims 1-44, 47-48, 51 and 58-71 under 35 USC § 103(a) as being unpatentable over EP 0 719 546 by itself is appropriate and is respectfully requested.

WO 99/13816 discusses a process for preparing specific gradient loaded liposomes – however WO 99/13816 does not prepare any liposomes that include an anthracycline chemotherapeutic agent. Accordingly, WO 99/13816 does not teach all the elements of the instant claims. Thus, it is respectfully submitted that the instant claims are not *prima facie* obvious over the disclosure of WO 99/13816. Withdrawal of the rejection of claims 1-44, 47-48,

51 and 58-71 under 35 USC § 103(a) as being unpatentable over WO 99/13816 by itself is appropriate and is respectfully requested.

Finally, neither EP 0 719 546 nor WO 99/13816 describe quenching a gradient loaded liposome that was prepared from an anthracycline chemotherapeutic agent. Accordingly, it is respectfully submitted that even if one skilled in the art found motivation to combine the teachings of EP 0 719 546 or WO 99/13816, *arguendo*, the combination would not have provided one skilled in the art with a reasonable expectation that gradient loaded liposomes including an anthracycline chemotherapeutic agent could be usefully quenched as recited in the instant claims. Thus, it is respectfully submitted that the instant claims are not *prima facie* obvious over the disclosure of EP 0 719 546 in combination with WO 99/13816. Withdrawal of the rejection of claims 1-44, 47-48, 51 and 58-71 under 35 USC § 103(a) as being unpatentable over EP 0 719 546 in combination with WO 99/13816 is appropriate and is respectfully requested since a *prima facie* case of obviousness does not exist.

Additionally, as discussed at page 6 lines 3-10 of the instant specification, WO 99/13816 does not teach or suggest that upon administration of the liposomal formulation, the original gradient can be attained. This property of the claimed liposomes makes them generally more useful, since the higher gradient prevents the therapeutic agent from leaking from the liposomes too quickly (please see the specification at page 14, bridging to page 15). Accordingly, the novel liposomes of the instant claims possess a beneficial property that is not described or appreciated in EP 0 719 546 or WO 99/13816. For this additional reason, it is respectfully submitted that the instant claims are not obvious over EP 0 719 546 in combination with WO 99/13816.

The Examiner has also rejected claims 7, 45-46 and 49 under 35 USC § 103(a) as being unpatentable over EP 0 719 546 or WO 99/13816, and further in view of Webb (5,814,335). This rejection is respectfully traversed.

At page 5 of the office action the Examiner stated that what is lacking in EP 0 719 546 and WO 99/13816 is the use of sphingomyelin as a liposome forming lipid. As discussed above, the independent claims 1, 63, and 71 are not obvious over the primary documents EP 0 719 546 and WO 99/13816 taken alone or in combination. It is respectfully submitted that the secondary document Webb does not cure the deficiencies discussed above, since it was only cited with respect to sphingomyelin as a liposome forming lipid. Accordingly, the instant claims are not

obvious over the disclosures of EP 0 719 546 and WO 99/13816, further in view of Webb (5,814,335). Withdrawal of this rejection is respectfully requested.

The Examiner has also rejected claims 52-57 under 35 USC § 103(a) as being unpatentable over EP 0 719 546 or WO 99/13816, further in view of Clerc (5,939,096). This rejection is respectfully traversed.

At page 6 of the office action the Examiner stated that what is lacking in EP 0 719 546 and WO 99/13816 is the teaching of dehydrating the liposomes in the presence of cryoprotectants. As discussed above, the independent claims 1, 63, and 71 are not obvious over the primary documents EP 0 719 546 and WO 99/13816 taken alone or in combination. It is respectfully submitted that the secondary document Clerc does not cure the deficiencies discussed above, since it was only cited with respect to dehydrating the liposomes in the presence of cryoprotectants. Accordingly, the instant claims are not obvious over the disclosures of EP 0 719 546 and WO 99/13816, further in view of Clerc (5,939,096). Withdrawal of this rejection is respectfully requested.

Obviousness-type Double Patenting Rejection

The Examiner has rejected claims 1-71 under the judicially created doctrine of obviousness-type double patenting over co-pending Application No. 10/723,431.

Since the instant office action was mailed, claim amendments have been submitted in co-pending Application No. 10/723,431. Accordingly, the propriety of the double patenting rejection can not be properly assessed at this time. Applicant will address any double patenting issues once otherwise allowable subject matter has been identified in both pending applications. Applicant thanks the Examiner for pointing out this potential issue.

The Examiner also rejected claims 1-71 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-31 and 35-64 of U.S. Patent No. 6,740,335 by itself or in combination with EP cited above. This rejection is respectfully traversed.

US Patent 6,740,335 is related to WO 99/13816. In the instant office action, the Examiner rejected the pending claims under 35 USC 103(a) as obvious over WO 99/13816 (see above). It is respectfully submitted that the instant claims are non-obvious over the claims of US 6,740,335 for the reasons presented above in response to the 35 USC 103(a) rejection over WO

99/13816. Accordingly, withdrawal of the obviousness type double patenting rejection over claims 30-31 and 35-64 of US Patent 6,740,335 is appropriate and is requested.

CONCLUSION

The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby. If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.

Respectfully submitted,

Ning Hu et al.

By their Representatives,

Viksnins Harris & Padys PLLP
Customer Number 53684
PO Box 111098
St. Paul, MN 55111-1098
(952) 876-4092

Date: 9-27-07

By: _____
Robert J. Harris
Reg. No. 37,346